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(71) Applicant *(for all designated States except US)*: **DEPUY PRODUCTS, INC.** [US/US]; 700 Orthopaedic Drive, Warsaw, IN 46581 (US).

(71) Applicants and
(72) Inventors: **BRUDER, Scott** [US/US]; 33 Crown Point Road, Sudbury, MA 01776 (US). **CLARKE, Rhonda** [US/US]; 2901 Lake John, Winona Lake, IN 46590 (US). **PEDROZO, Hugo** [CO/US]; 2113 E 1200 South, Silver Lake, IN 46982 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **PLOUHAR, Pamela, Lynn** [US/US]; 17411 Battles Road, South Bend, IN 46614 (US).

(74) Agents: **COFFEY, William, R.** et al.; Barnes & Thornburg, 11 South Meridian Street, Indianapolis, IN 46204 (US).

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(54) Title: FLOWABLE OSTEOGENIC AND CHONDROGENIC COMPOSITIONS

(57) Abstract: The repair of a cartilage or bone defect is described using a flowable compositions including a chondrogenic agent or osteogenic agent and a biocompatible carrier that is more fluid at ambient temperatures than at elevated temperatures.

FLOWABLE OSTEOGENIC AND CHONDROGENIC COMPOSITIONS

CROSS REFERENCE TO RELATED APPLICATIONS

This non-provisional patent application claims priority to a provisional patent application, serial number 60/331,610 filed November 20, 2001.

FIELD

The present invention relates to the repair of cartilage and bone. In particular, the present invention relates to the repair of cartilage and bone using a flowable composition comprising an osteogenic agent or a chondrogenic agent and a suitable carrier.

BACKGROUND

The body typically reacts quickly to defects in bone, such as those resulting from injury, infection, malignancy, or developmental malformation. In fact, the processes of bone repair work well under normal circumstances. Moreover, even when the natural processes fail, a good repair may be still achieved using simple methods of immobilization. Nevertheless, a number of scenarios exist where these natural repair processes fail to correct the defect or fail to yield good quality bone. In particular, fractures at risk of delayed union, nonunion, or malunion often fail to heal correctly. A fracture that takes longer to heal than expected is a delayed union, while a fracture that fails to heal in a reasonable amount of time, usually greater than 6 to 12 months, is termed a nonunion. A malunion may occur when a fracture does not heal with a normal alignment. In general, such fractures may either fail to ever heal, or fail to provide sufficient bone quality allowing the resumption of normal activities. Furthermore, bone defects, such as step defects, pits, surface abnormalities, and the like, that are not associated with fractures may also fail to heal correctly. Since movement within a bone defect, such as a fracture, may serve to stimulate the processes of repair, defects in bone not arising from a fracture, like step defects, pits, and surface abnormalities, may also require an undesirable length of time to heal.

In contrast to bone, many defects in cartilage arising from injury, infection, malignancy, or developmental malformation, often fail to heal with normal cartilage tissue. Such defects include Grade III and Grade IV (osteochondral) cartilage lesions that

can be caused by traumatic injury to a joint or upon the removal of graft tissue used to treat other sites, such as donor sites in osteochondral grafting. In addition, such lesions or defects can be created during the treatment of tumors involving articular surfaces, or during the removal of cysts.

The failure to repair bone and cartilage defects often results in pain, instability, and an associated loss of function of the involved limb. Fractures occurring in young, productive individuals that fail to heal or fail to heal properly can result in permanent life-altering disabilities, diminishing the quality of life. Similarly, fracture and other types of defects occurring in the elderly can cause chronic pain and lead to instability having exacerbated consequences to an already physically-challenged group.

When standard external immobilization is insufficient, clinical approaches for healing fractures involving a variety of surgical procedures designed to stabilize the fracture, incorporating techniques of internal fixation are often performed. Existing bone may be supplemented with bone autografts, as well as bone allografts or other synthetic materials, to provide the necessary internal fixation. Such bone supplementation may also be performed in conjunction with other artificial prostheses and implants. These artificial prostheses for internal fixation may provide structural stability and may be fabricated from many materials, for example metals such as stainless steel, cobalt-chromium-molybdenum alloys, titanium, and the like. In addition to the above-described fixation and prosthetic methods, the simultaneous stimulation of new bone formation may be performed using various agents, including bioceramics, polymers, such as poly(lactic acid)/poly(glycolic acid) copolymers, and natural substances, such as collagen and hydroxyapatite, as described in U.S. Patent Nos. 6,071,530, 5,385,887, 4,578,384, 4,563,489, 4,637,931, 4,578,384, 6,162,225, 5,181,926, and 5,084,051. Semi-solid materials, such as gels and pastes, have also been used. For example, DYNAGRAFT™ (GenSci Regeneration Laboratories, Inc., Irvine, CA), incorporates demineralized bone matrix (DBM), cancellous bone chips, or mineralized bone into a poloxamer. These GenSci products are available as a gel or putty for use in a surgical setting.

The introduction of graft materials and prostheses like those described typically involves a surgical operation. However, in certain circumstances, specialized materials can be introduced into the defect site using less invasive procedures, such as introduction by injection. Among such injectable compositions are the non-sintered

bioceramics found in U.S. Patent Nos. 6,214,368, 6,165,486, and 5,782,971, allograft demineralized bone paste formulations, and the collagen compositions described in U.S. Patent Nos. 5,290,558, 5,510,396, and 5,328,955. In addition, U.S. Patent No. 4,645,503 discloses production of a moldable bone implant material containing approximately 65-95% hard filler particles and a binder composed of approximately 35-50% of a biocompatible, biodegradable thermoplastic polymer which has fluid flow properties at about 60 °C.

Other methods aimed at avoiding surgery in the repair of bone defects involve agents which are free from a support structure. Such agents known to facilitate fracture healing may be introduced locally to the defect site by injection, or alternatively administered systemically. However, systemic administration can be limited by the ability to selectively target the therapeutic substance to a particular site.

A non-operative, minimally invasive introduction or administration of a composition capable of promoting bone or cartilage repair, that will also exhibit a desirable residence time at the defect site is desired.

SUMMARY

There is provided a flowable composition for introduction to a bone or cartilage defect comprising an osteogenic agent or chondrogenic agent, where the osteogenic agent or chondrogenic is an inhibitor of bone resorption or a bone anabolic agent, and a biocompatible carrier that is more fluid at ambient temperature than at an elevated temperature.

There is also provided a flowable composition for introduction to a bone or cartilage defect comprising an osteogenic agent or chondrogenic agent, where the osteogenic agent or chondrogenic is a protein, a non-native protein, a protein fragment, or a peptide, and a biocompatible carrier that is more fluid at ambient temperature than at an elevated temperature.

There is also provided a flowable composition for introduction to a bone or cartilage defect comprising an osteogenic agent or chondrogenic agent, where the agent is a bone marrow cell, a genetically-modified cell, or a population of bone marrow cells or genetically-modified cells, and a biocompatible carrier that is more fluid at ambient temperature than at an elevated temperature.

In some illustrative embodiments, the agent is an inhibitor of bone resorption, such as estrogen, selective estrogen receptor modifiers, bisphosphonates, *src*-tyrosine kinase inhibitors, cathepsin K inhibitors, vacuolar-ATPase inhibitors, or analogs or derivatives thereof. In other illustrative embodiments, the agent is a bone anabolic agent, such as statins, fluprostenol, vitamin D, prostaglandins, or analogs or derivatives thereof.

In other illustrative embodiments, the agent is a bone cell stimulating factor (BCSF), chrysalin, KRX-167, MP52, or an analog or derivative thereof. In other illustrative embodiments, the composition is substantially free of the bone morphogenetic protein-2 (BMP-2).

Carriers useful with the above agents include poloxamers, hydrogels, and block copolymers, including pluronic F127, as known as poloxamer 407, pluronic F108, pluronic F98, and the like. The carriers may be block copolymers of poly(propylene oxide) and poly(ethylene oxide), including block copolymers having a poly(propylene oxide) fragment having a molecular weight in the range from about 900 to about 4000. The block copolymer may have poly(ethylene oxide) fragments comprising from about 70% to about 80% by weight of the block copolymer.

In particular, carriers having the formula:

$HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_cH$,

where a, b, and c are integers, are useful with the above agents. The carrier may comprise from about 5% to about 99% of the composition.

The compositions may also include a bioactive component such as collagen, collagen lattices and insoluble collagen derivatives, hydroxyapatite, tricalcium phosphate, calcium phosphate, radio-opacifying agents, carboxymethylcellulose, hydroxyethylcellulose, sodium alginate, xanthan gum, and hyaluronic acid or salts thereof.

Other bioactive components are salicylic acid, acetaminophen, ibuprofen, naproxen, piroxicam, flurbiprofen, morphine, cocaine, lidocaine, bupivacaine, xylocaine, and benzocaine.

Still other bioactive components include amino acids, peptides, vitamins, inorganic elements, co-factors for protein synthesis, hormones, enzymes, nerve growth promoting substances, fibronectin, growth hormones, colony stimulating factors,

cytokines, interleukin-1, angiogenic drugs and polymeric carriers containing such drugs, biocompatible surface active agents, anti-thrombotic drugs, cytoskeletal agents, natural extracts, bioadhesives, antitumor agents, antineoplastic agents, tumor-specific antibodies conjugated to toxins, tumor necrosis factor, cellular attractants and attachment agents, immuno-suppressants, permeation and penetration enhancers, blood, blood cells, and nucleic acids.

There is also provided a flowable composition for introduction to a bone or cartilage defect comprising an osteogenic agent or chondrogenic agent that is substantially free of the bone morphogenetic protein BMP-2, and a biocompatible carrier that is more fluid at ambient temperature than at an elevated temperature.

Finally, there is provided a method for repairing a bone or cartilage defect comprising administering a composition described herein in an amount effective to enhance the repair of the bone or cartilage defect. The compounds may be administered by injection.

Such defects include fractures, fractures at risk of non-union, defects in bone or cartilage caused by the removal of a tumor or cyst, defects in bone or cartilage associated with a joint prosthesis, osteotomy defects associated with treatment of a mal-alignment or a deformation, defects in bone or cartilage cased by trauma or degeneration, defects in bone or cartilage associated with a spinal alignment or spinal fusion procedure, and oral-maxillofacial, cranio-facial, and periodontal defects.

DETAILED DESCRIPTION

The term "osteogenic agent" as used herein refers to agents that promote, induce, stimulate, generate, or otherwise effect the production of bone or the repair of bone. The presence of an osteogenic agent in the defect site may elicit an effect on the repair of the defect in terms of shortening the time required to repair the bone, by improving the overall quality of the repair, where such a repair is improved over situations in which such osteogenic agents are omitted, or may achieve contemporaneously both shortened repair times and improved bone quality. It is appreciated that osteogenic agents may effect bone production or repair by exploiting native or endogenous systems, such as by the inhibition of bone resorption.

The term "chondrogenic agent" as used herein refers to agents that promote, induce, stimulate, generate, or otherwise effect the production of cartilage or the

repair of cartilage. The presence of a chondrogenic agent in the defect site may elicit an effect on the repair of the defect in terms of shortening the time required to repair the cartilage, by improving the overall quality of the repair, where such a repair is improved over situations in which such chondrogenic agents are omitted, or may achieve contemporaneously both shortened repair times and improved cartilage quality. It is appreciated that chondrogenic agents may effect cartilage production or repair by exploiting native or endogenous systems, such as by the inhibition of cartilage breakdown.

Although specificity between the stimulation of bone growth by an osteogenic agent or the stimulation of cartilage growth by a chondrogenic agent is desired in some situations, it is appreciated that an agent having the capability to stimulate both bone growth and cartilage growth may be desired for certain situations. Such an agent capable of stimulating both bone and cartilage growth is contemplated to fall within the scope of the present invention.

The term "flowable" as used herein refers to the ability of a material to flow either of its own accord or under the influence of a mechanical force, such as may be exerted by the plunger element of a syringe. Compositions of paste-like or putty-like consistency as well as those of liquid or runny consistency are properly referred to as flowable. The term also applies to compositions whose consistencies allow a shape-sustaining character, but are still readily deformable. Specific forms of flowable compositions include cakes, pastes, putties, creams, fillers, and liquids.

Osteogenic agents may promote bone growth by acting as bone anabolic agents, or bone antiresorptive agents. Chondrogenic agents may promote cartilage growth by acting as cartilage anabolic agents, or cartilage antiresorptive agents. Compositions of the present invention may also effect repair of the bone or cartilage defect by stabilizing the defect to promote healing. The ramifications of using such osteogenic or chondrogenic agents include increased healing rates, effecting a more rapid new bone or cartilage ingrowth, improved repair quality or improved overall quality of the resulting bone or cartilage.

Cartilage repairing compositions employing one or more small molecules, one or more large molecules, a cell or a population of one or more cells or cell-types exhibiting a chondrogenic capability are described herein. In addition, chondrogenic

agents comprising a combination of such small molecules, large molecules, and cell populations are also contemplated.

Bone repairing compositions employing one or more small molecules, one or more large molecules, a cell or a population of one or more cells or cell-types exhibiting an osteogenic capability are described herein. In addition, osteogenic agents comprising a combination of such small molecules, large molecules, and cell populations are also contemplated.

In one embodiment the osteogenic agent or chondrogenic agent is a "small molecule" such as a synthetic molecule, drug, or pharmaceutical involved in or important to bone or cartilage biology, including statins, such as lovastatin, simvastatin, atorvastatin, and the like, fluprostenol, vitamin D, estrogen, a selective estrogen receptor modifier, a bisphosphonate, such as allendronate, ibandronate, and the like, a *src*-tyrosine kinase inhibitor, a cathepsin K inhibitor, a vacuolar-ATPase inhibitor, a prostaglandin, such as PGE-2, hydroxyapatite, tricalcium phosphate, and analogs and derivatives thereof. Combinations of such small molecules in providing the osteogenic or chondrogenic agent are contemplated herein.

In one aspect, the small molecule, drug, or pharmaceutical is a compound that slows the resorption of bone or cartilage by metabolic or physiological processes. Such compounds may be bone or cartilage resorption inhibitors or other anti-resorptive agents. In another aspect, the small molecule, drug, or pharmaceutical is a compound that induces the proliferation of bone or cartilage, or induces or conducts bone or cartilage in-growth. Such agents may be bone or cartilage anabolic agents.

In another embodiment, the osteogenic agents are compounds active at the nicotine acetylcholine receptor (ACR), such as the nicotinic ACR present in endothelial cells. It is appreciated that the nicotinic ACR is involved in the neovascularization of the implanted composition. The promotion of vascular tissue may be a precursor event to the induction of new bone formation. Such neovascularization may be accomplished by including nicotinic ACR agonists. Known nicotinic agonists in combination with the herein described carriers are contemplated as illustrative osteogenic compositions.

In another embodiment the osteogenic agent or chondrogenic agent is a "large molecule" such as protein, an enzyme, a peptide, a receptor ligand, a peptide hormone, lipid, or carbohydrate involved in, or important to, bone or cartilage

physiology, including chrysalin, osteogenic growth peptide (OGP), bone cell stimulating factor (BCSF), KRX-167, MP52, gastric decapeptide, parathyroid hormone (PTH), a fragment of parathyroid hormone, osteopontin, osteocalcin, a fibroblast growth factor (FGF), such as basic fibroblast growth factor (bFGF) and FGF-1, osteoprotegerin ligand (OPGL), platelet-derived growth factor (PDGF), an insulin-like growth factor (IGF), such as IGF-1 and IGF-2, vascular endothelial growth factor (VEGF), transforming growth factor (TGF), such as TGF-alpha and TGF-beta, epidermal growth factor (EGF), growth and differentiation factor (GDF), such as GDF-5, GDF-6, and GDF-7, thyroid-derived chondrocyte stimulation factor (TDCSF), vitronectin, laminin, amelogenin, amelin, fragments of enamel, or dentin extracts, bone sialoprotein, and analogs and derivatives thereof. Combinations of such large molecules in providing the osteogenic or chondrogenic agent are contemplated herein.

The bone morphogenic proteins, or BMPs, comprise a subset of prteins from the TGF-beta super family of proteins. Several of these BMPs have been implicated in bone and cartilage physiology, including *BMP*-1, *BMP*-2, *BMP*-3, *BMP*-4, *BMP*-5, *BMP*-6 and *BMP*-7, disclosed in U.S. Pat. Nos. 5,108,922; 5,013,649; 5,116,738; 5,106,748; 5,187,076; and 5,141,905; *BMP*-8, disclosed in PCT publication WO91/18098; and *BMP*-9, disclosed in PCT publication WO93/00432, *BMP*-10, disclosed in PCT application WO94/26893; *BMP*-11, disclosed in PCT application WO94/26892, or *BMP*-12 or *BMP*-13, disclosed in PCT application WO 95/16035, or *BMP*-15, disclosed U.S. Pat. No. 5,635,372, the disclosure or each is incorporated herein by reference.

In one aspect, the osteogenic agents and chondrogenic agents described herein are non-native proteins, enzymes, or peptides. Such non-native proteins include proteins produced in exogenous systems, such as genetically-modified cells, and recombinant proteins, like MP52, also known as BMP-14 or rhGDF-5, or other proteins isolated from genetically-modified cells and tissues. Proteins that have been modified by chemical synthesis are also included. In addition, it is understood that non-native proteins include proteins that are prepared by chemical synthesis.

In another aspect, the osteogenic agents and chondrogenic agents described herein are protein fragments or peptides that are prepared by chemical synthesis or by proteolysis of other proteins. Such proteolysis may be either chemical or

enzymatic. In some cases, these protein fragments or peptides may be compounds that do not typically occur as a result of typically-encountered or normal metabolic and physiological processes. Illustratively, the thrombin fragment TP508, also known as chrysalin is representative of such protein fragments and peptides.

In another embodiment, the osteogenic agents and chondrogenic agents are nuclear transcription factors or inhibitors of nuclear transcription factor binding in combination with cells, especially cells from the host or subject. Such nuclear transcription factors regulate the transcription of certain genes. In one aspect, the osteogenic agents and chondrogenic agents are inhibitors of the binding of peroxisome proliferator-activated receptors (PPAR), such as PPAR-α, PPAR-γ, and PPAR-δ. It is appreciated that blocking the binding of PPAR may drive more precursor cells into the osteoblast lineage rather than to other mesenchymal lineages. In particular, PPAR-γ is thought to be required for recruitment of mesenchymal cells into the adipocyte lineage. Thus, PPAR binding is involved in, and may be required for adipogenesis. As PPAR binding is blocked, more precursor cells will mature into osteoblasts. In addition, compounds that bind directly to transcription factors or transcription regulators implicated in recruiting precursor or mesenchymal cells are also contemplated as osteogenic and chondrogenic agents to be included in the compositions described herein. Examples include, but are not limited to SOX-9, SOX-5, CBFA-1 (RUNX-2), and the like. Such binders of transcription factors or transcription regulators are capable of modulating or stimulating the expression of certain genes.

Osteogenic agents and chondrogenic agents described herein may also be substantially free of the bone morphogenetic protein BMP-2. It is well-known that BMP-2 causes osteoprogenitor cells to differentiate into osteoblast-like cells, the cells that deposit and mineralize new bone. As used herein in conjunction with the presence of the bone morphogenetic protein BMP-2, the term "substantially free" refers to levels of BMP-2 so reduced that effects on the bone or cartilage defect following the introduction of the osteogenic or chondrogenic agents described herein are likely not attributable to BMP-2. However, it is appreciated that the complete preclusion of BMP-2 from the osteogenic or chondrogenic agent may not be accomplished in certain circumstances, or when using certain sources of the osteogenic or chondrogenic agent.

In another embodiment the osteogenic agent or chondrogenic agent is a cell or population of cells involved in, or important to, bone or cartilage biology, such as pluripotent stem cells, autologous, allogenic, or xenogeneic progenitor cells, osteoblasts, chondrocytes, adipose-derived stem cells, bone marrow cells, mesenchymal stem cells, homogenized or comminuted tissue transplants, genetically transformed cells, and the like. Combinations of such cell populations in providing the osteogenic or chondrogenic agent are also contemplated herein.

Carriers of the present invention are desirably bio-compatible, bio-absorbable materials with low host toxicity, low irritative properties, and have a low potential for antigenicity. Suitable carriers include, but are not limited to, poly(ethylene oxide), poly(propylene oxide), polyoxyalkylenes, poloxamers, hydrogels, block copolymers, including reverse-phase block copolymers, such as poly(ethylene oxide)-poly(propylene oxide) copolymers and the like. Illustrative block copolymers are of the following general structure:

$$HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_cH$$

where a, b, and c are integers. Typical values for the integers a, b, and c, may be selected to provide block copolymers where the poly(ethylene oxide) fragment comprises a particular percent range of the total molecular weight, or alternatively, the integers a, b, and c may be selected to provide a particular range of total molecular weight of the block copolymer, such as those resulting in a molecular weight in the range from about 4700 to about 14600 g/mol. Illustrative examples include block copolymers according to the above formula where the integer a is in the range from about 75 to about 125, the integer b is in the range from about 55 to about 85, and the integer c is in the range from about 75 to about 125.

Block copolymers of poly(ethylene oxide)-poly(propylene oxide) refer generically to non-ionic surface active agents of a polymer type having a relatively hydrophobic poly(propylene oxide) fragment bracketed or blocked by a pair of relatively hydrophilic poly(ethylene oxide) fragments. Block copolymers are distinguished by this bracketed arrangement of the homopolymer components. It may be feasible to prepare surface active agents having various properties by changing either the molecular weight of the block copolymer or the relative molecular weight of the poly(propylene oxide) fragment, thereby altering the corresponding mixing ratio thereof, to the ethylene oxide.

The poly(ethylene oxide) fragments illustratively may comprise from about 70% to about 80% of the total weight of the carrier. It is appreciated that various ranges of the weight percentage of the poly(ethylene oxide) fragments of the block copolymer may impart properties associated with toxicity, and solubility, especially water solubility.

Importantly, it is appreciated that the weight percent range of the poly(ethylene oxide) fragments affects the stability of the gel at a given temperature. Block copolymers, such as the PLURONIC® block copolymers, including but not limited to F127, F108, and F98, often exhibit reverse-phase properties, such as reversible temperature-dependent sol-gel transitions. Such block copolymers form gels at body temperature, while remaining liquid or substantially fluid at ambient temperature. Illustrative examples of block copolymers include those where the molecular weight of the poly(propylene oxide) fragment is in the range from about 900 to about 4000, or in the range from about 1500 to about 4000, and where the percent by weight of the ethylene oxide fragment in the total block copolymer molecule is about 70%. Illustratively, the poly(ethylene oxide)-poly(propylene oxide) block copolymer PLURONIC®-F127 (BASF Corp., Mt. Olive, NJ), also known as poloxamer 407, with a molecular weight of about 12,600 g/mol, is a suitable carrier composed mostly (70% by weight) of poly(ethylene oxide).

It is appreciated that the flowable carrier may be made up of one or more liquid polyhydroxy compounds or derivatives in solution with one or more solid polyhydroxy compounds or derivatives. Carriers may further include physiologically relevant solvents such as water, physiological saline, ethanol, glycerol, or glucose. In addition, carriers may include additives such as propylene glycol, polypropylene glycol, ethylene glycol, polyethylene glycol, or mixtures thereof, to adjust the flowable properties of the composition. Other illustrative examples of additional carrier components include other F-series PLURONIC™ block copolymers. Functionally, the carrier component of the composition serves to provide a flowable material of widely varying consistency. It is appreciated that changes to the concentration of the block copolymer can also affect the flowable properties of the composition. The carrier may comprise from about 5% to about 99%, or from about 16% to about 40% of the composition, depending on the application in which it is used and the choice of the carrier. In other illustrative embodiments the carrier comprises about 5% to about 90%, about 10% to about 90%, or

about 10% to about 50% of the composition. It is appreciated that the level of carrier component may be adjusted to maintain the flowable nature of the composition at ambient temperature and the corresponding decrease on flowability at elevated temperatures.

Components that provide additional structure to or generally reduce the fluidity of the flowable composition are also contemplated. Such components include collagen, collagen lattices and insoluble collagen derivatives, hydroxyapatite, cartilage fragments, calcium phosphate, radio-opacifying agents, carboxymethylcellulose, hydroxyethylcellulose, sodium alginate, xanthan gum, hyaluronic acid or a salt thereof, and the like. Such additional components may be added in conjunction with other ingredients described herein in order to balance an increase in the flowability of the osteogenic or chondrogenic composition upon the addition of other ingredients in variations of the herein-described compositions. For example, it is appreciated that the addition of such components, as well as the other additional components described herein, such as cells, proteins, carbohydrates, and the like, as well as other liquids, may considerably affect the consistency and gelling temperature of the composition, and thus, may require adjustment of the final carrier concentration in the composition to compensate for these additives.

The flowable osteogenic and chondrogenic compositions described herein are capable of being introduced to the defect site via multiple formats. Such flowable formats are advantageously delivered, applied, or otherwise introduced to the defect site without necessarily requiring surgery. It is appreciated that in some cases surgery is desirable to introduce the composition in variations of the process of the present invention. In particular, arthroscopic surgery and other minimally invasive surgical techniques are suitable means for delivering the flowable osteogenic agents and chondrogenic agents described herein. Delivery of flowable formats may be accomplished by a variety of known means, such as by injection via a cannula, catheter, syringe, syringe with a needle, pressure applicator, pump, and the like, or via a combination thereof. It is further appreciated that such modes of delivery allow positioning of the osteogenic composition or chondrogenic composition even in defect sites in challenging locations or situations.

Such compositions further allow a sustained disposition or sustained residence time of the accompanying osteogenic agent or chondrogenic agent within the defect site. Such sustained times in the defect site may be due to a degree of protection provided to the osteogenic agent or chondrogenic agent by the biocompatible carrier. Such protection may minimize exposure of the agent to routes of excretion, degradation via metabolism, non-target organs or tissues, or other processes that tend to reduce the effective concentration of the agent at the defect site. Such residence times are conveniently chosen in an end-use dependent manner, illustratively to allow sufficient time for the osteogenic agent or chondrogenic agent to effectively enhance bone or cartilage repair.

An embodiment includes an injectable format of such an osteogenic composition or chondrogenic composition. Particularly illustrative are carriers that undergo a temperature dependent sol-gel phase transition. Compositions employing carriers that are substantially liquid at ambient temperatures and semi-solid at body temperature are contemplated. Such carriers may especially serve to promote the achievement of prolonged residence times of the osteogenic agent or chondrogenic agent in the defect site, as described herein.

The term "ambient temperature" as used herein refers to a temperature range from about 1 °C to about 30 °C, or a range from about 4 °C to about 25 °C. Elevated temperatures include "body temperature." The term "body temperature" as used herein refers to the normal temperature range observed in various mammalian species, typically in the range from about 30 °C to about 40 °C, or illustratively about 37 °C.

Illustrative compositions may be injectable liquids or gels at ambient temperatures at the time of administration and may form gels, solids, or semi-solids at body temperatures within short periods of time after administration. Advantageously, the moldability of the composition prior to gel, solid, or semi-solid formation, allows the composition to conform to irregularities, crevices, cracks, holes, and the like, in the implant site.

In one aspect, the osteogenic composition or chondrogenic composition exhibits the ability to maintain its cohesiveness and resist erosion subsequent to being applied or introduced to an osseus or cartilaginous defect site. In an alternate aspect, desirable bioerosion can take place within a time-frame in an end-use dependent manner

consistent with effective bone or cartilage repair. It is appreciated that such relative ranges of bioerosion may be selected in an end-use dependent manner with routine experimentation.

Any of a variety of medically or surgically useful substances can also be incorporated into the flowable osteogenic or chondrogenic compositions described herein. These additional bioactive substances, agents, or components may be added to the osteogenic agent or chondrogenic agent component, added to the carrier component, or added to the osteogenic or chondrogenic composition once formed. It is contemplated that such additives may serve to reduce barriers to repair and thus maximize the potential of the osteogenic or chondrogenic agent.

Components that are capable of preventing infection in the host, either systemically or locally at the defect site, are contemplated as illustrative bioactive agents, substances, or components. These agents include anti-inflammatory agents, such as hydrocortisone, prednisone, and the like, NSAIDS, such as acetaminophen, salicylic acid, ibuprofen, and the like, selective COX-2 enzyme inhibitors, antibacterial agents, such as penicillin, erythromycin, polymyxin B, viomycin, chloromycetin, streptomycins, cefazolin, ampicillin, azactam, tobramycin, cephalosporins, bacitracin, tetracycline, doxycycline, gentamycin, quinolines, neomycin, clindamycin, kanamycin, metronidazole, and the like, antiparasitic agents such as quinacrine, chloroquine, vidarabine, and the like, antifungal agents such as nystatin, and the like, antiviricides, particularly those effective against HIV and hepatitis, and antiviral agents such as acyclovir, ribarivin, interferons, and the like.

Systemic analgesic agents such as salicylic acid, acetaminophen, ibuprofen, naproxen, piroxicam, flurbiprofen, morphine, and the like, and local anesthetics such as cocaine, lidocaine, bupivacaine, xylocaine, benzocaine, and the like, are also contemplated as bioactive components suitable as additives.

Other bioactive components that may enhance the overall effectiveness of the osteogenic or chondrogenic agent include amino acids, peptides, including peptide fragments of the various bone morphogenetic proteins, vitamins, inorganic elements, co-factors for protein synthesis, hormones, enzymes such as collagenase, peptidases, oxidases, and the like, angiogenic drugs and polymeric carriers containing such drugs, biocompatible surface active agents, anti-thrombotic drugs, cytoskeletal agents, natural

extracts, bioadhesives, antitumor agents, antineoplastic agents, such as methotrexate, 5-fluorouracil, adriamycin, vinblastine, cisplatin, and the like, tumor-specific antibodies conjugated to toxins, tumor necrosis factor, cellular attractants and attachment agents; immuno-suppressants, permeation and penetration enhancers, such as fatty acid polyethylene glycol monoesters of laureate, myristate, stearate, and the like, and nucleic acids. The amounts of such added substances can vary widely with optimum levels being readily determined for a given case by routine experimentation.

Still other bioactive components, or metabolic precursors thereof, that are capable of promoting growth and survival of cells and tissues, or augmenting the functioning of cells, are contemplated, and include nerve growth promoting substances, such as a ganglioside, nerve growth factor, and the like, fibronectin (FN), growth hormones, such as somatotropin, human growth hormone (HGH), and the like, colony stimulating factors, cytokines, and interleukin-1 (IL-1).

Methods for repairing a bone or cartilage defect, using the compositions described herein are also provided. Such methods comprise the step of introducing to the cartilage or bone defect site a flowable composition, as described herein, comprising an effective amount of an osteogenic agent or chondrogenic agent incorporated in a biocompatible carrier, to promote, induce, stimulate, repair, or otherwise generate new bone or new cartilage growth at the site, or at sites proximal to the site of administration.

The amount of the osteogenic agent used in the methods described herein should be an amount effective to elicit bone-inducing, bone-promoting, bone-stimulating, or bone-generating properties. Similarly, the amount of chondrogenic agent used in the methods described herein should be an amount effective to elicit cartilage-inducing, cartilage-promoting, cartilage-stimulating, or cartilage-generating properties. Amounts of osteogenic agent or chondrogenic agent conforming to ultimate doses from about 1 ng to about 15 mg per unit volume carrier are not unusual.

Introduction of the foregoing osteogenic compositions or chondrogenic compositions to the site of a bone or cartilage defect, resulting from injury, infection, malignancy, developmental malformation, and the like, desirably leads to the repair of the defect by promoting new bone or new cartilage growth. Examples of such defect sites of introduction include acute fractures, especially fractures at risk of forming non-unions, mal-unions, delayed unions, step defects, and other tissue defects, such as tissue

regeneration sites, sites of tumor or cyst removal, osteotomies used to treat mal-alignment or other deformations, and defects created by osteolysis around total joint replacements. Such bone defects may be treated anywhere in the skeleton. Illustrative treatment sites include sites of long bone defects and fractures, sites of knee, hip, shoulder, and other joint prostheses, sites of spinal repair, such as spinal fusion, and other alignment defects, and oral-maxillofacial, cranio-facial, and periodontal defects.

The osteogenic composition can be utilized for a variety of orthopedic, neurosurgical, and oral or maxillofacial surgical procedures such as the repair of simple and compound fractures, non-unions requiring external or internal fixation, joint reconstructions such as arthrodesis, general arthroplasty, cup arthroplasty of the hip, femoral and humeral head replacement, femoral head surface replacement and total joint replacements, repairs of the vertebral column including spinal fusion and internal fixation, tumor surgery, such as deficit filling, disectomy, laminectomy, anterior cervical and thoracic operations, repair of spinal injuries, and spinal deformities, such as scoliosis, lordosis, and kyphosis treatments, intramedullary fixation of fractures, mentoplasty, temporomandibular joint replacement, alveolar ridge augmentation and reconstruction, inlay bone grafts, implant placement and revision, sinus lifts, and the like.

The osteogenic compositions and chondrogenic compositions described herein can be readily prepared when and as needed, preferably with the components of the composition, the means for their combination to provide the composition, and the means for applying the composition to a bone defect site being provided in the form of a unitary kit. Alternatively, the osteogenic compositions and chondrogenic compositions can be prepared before immediate use and may be stored in a sterile condition for later use, optionally within the means which will be used to introduce the osteogenic composition or chondrogenic composition to the bone or cartilage defect site.

It is appreciated that the osteogenic compositions and chondrogenic compositions and methods of using such compositions described herein may be combined for use in conjunction with conventional methods for repairing bone and cartilage defects, such as prostheses, and the like.

WHAT IS CLAIMED IS:

1. A flowable composition for introduction to a bone or cartilage defect comprising:

an osteogenic agent or chondrogenic agent, where said agent is selected from the group consisting of inhibitors of bone resorption and bone anabolic agents, and

a biocompatible carrier, where said biocompatible carrier is more fluid at ambient temperature than at an elevated temperature.

2. The composition of claim 1, wherein the agent is selected from the group consisting of estrogen, selective estrogen receptor modifiers, bisphosphonates, *src*-tyrosine kinase inhibitors, cathepsin K inhibitors, and vacuolar-ATPase inhibitors, and analogs and derivatives thereof.

3. The composition of claim 1, wherein the agent is selected from the group consisting of statins, fluprostenol, vitamin D, and prostaglandins, and analogs and derivatives thereof.

4. The composition of claim 1, wherein the agent is substantially free of the bone morphogenetic protein BMP-2.

5. The composition of claim 1, wherein the agent is substantially free of the bone morphogenetic proteins.

6. A flowable composition for introduction to a bone or cartilage defect comprising:

an osteogenic agent or chondrogenic agent, where said agent is selected from the group consisting of proteins, protein fragments, and peptides, and

a biocompatible carrier, where said biocompatible carrier is more fluid at ambient temperature than at an elevated temperature.

7. The composition of claim 6, wherein the agent is a non-native protein.

8. The composition of claim 6, wherein the agent is selected from the group consisting of chrysalin, KRX-167, and MP52, and analogs and derivatives thereof.

9. The composition of claim 6, wherein the agent is selected from the group consisting of bone cell stimulating factor, thyroid-derived chondrocyte stimulation factor, and vascular endothelial growth factor, and analogs and derivatives thereof.

10. The composition of claim 6, wherein the agent is substantially free of the bone morphogenetic protein BMP-2.

11. The composition of claim 6, wherein the agent is substantially free of the bone morphogenetic proteins.

12. A flowable composition for introduction to a bone or cartilage defect comprising:

an osteogenic agent or chondrogenic agent, where said agent is a bone marrow cell, a genetically-modified cell, or a population of bone marrow cells or genetically-modified cells, and

a biocompatible carrier, where said biocompatible carrier is more fluid at ambient temperature than at an elevated temperature.

13. The composition of claim 1, 6, or 12, wherein the carrier is a poloxamer, hydrogel, or block copolymer.

14. The composition of claim 13, wherein the carrier is poloxamer 407.

15. The composition of claim 13, wherein the carrier is a block copolymer of poly(propylene oxide) and poly(ethylene oxide).

16. The composition of claim 15, wherein the block copolymer has a poly(propylene oxide) fragment having a molecular weight in the range from about 900 to about 4000.

17. The composition of claim 15, wherein the block copolymer has poly(ethylene oxide) fragments comprising from about 70% to about 80% by weight of the block copolymer.

18. The composition of claim 13, wherein the carrier is a compound of the formula:

$HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_cH$,

where a, b, and c are integers.

19. The composition of claim 1, 6, or 12, wherein the carrier comprises from about 5% to about 99% of the composition.

20. The composition of claim 1, 6, or 12, further comprising a bioactive component.

21. The composition of claim 20, wherein the bioactive component is selected from the group consisting of collagen, collagen lattices and insoluble collagen

derivatives, hydroxyapatite, tricalcium phosphate, calcium phosphate, radio-opacifying agents, carboxymethylcellulose, hydroxyethylcellulose, sodium alginate, xanthan gum, and hyaluronic acid or salts thereof.

22. The composition of claim 20, wherein the bioactive component is selected from the group consisting of salicylic acid, acetaminophen, ibuprofen, naproxen, piroxicam, flurbiprofen, morphine, cocaine, lidocaine, bupivacaine, xylocaine, and benzocaine.

23. The composition of claim 20, wherein the bioactive component is selected from the group consisting of amino acids, peptides, vitamins, inorganic elements, co-factors for protein synthesis, hormones, enzymes, nerve growth promoting substances, fibronectin, growth hormones, colony stimulating factors, cytokines, interleukin-1, angiogenic drugs and polymeric carriers containing such drugs, biocompatible surface active agents, anti-thrombotic drugs, cytoskeletal agents, natural extracts, bioadhesives, antitumor agents, antineoplastic agents, tumor-specific antibodies conjugated to toxins, tumor necrosis factor, cellular attractants and attachment agents, immuno-suppressants, permeation and penetration enhancers, blood, blood cells, and nucleic acids.

24. A flowable composition for introduction to a cartilage or bone defect site comprising:

an osteogenic agent or chondrogenic agent, where said agent is substantially free of the bone morphogenetic protein BMP-2, and

a biocompatible carrier, where said biocompatible carrier is more fluid at ambient temperature than at an elevated temperature.

25. A method for repairing a bone or cartilage defect comprising administering a composition recited in claim 1, 6, or 12 to the bone or cartilage defect, said composition administered in an amount effective to enhance the repair of the bone or cartilage.

26. The method of claim 25, wherein the administering step includes administering the composition to the cartilage or bone defect by injection.

27. The method of claim 25, wherein the administering step includes administering the composition to the bone or cartilage defect, where said bone or cartilage defect is selected from the group consisting of fractures, fractures at risk of non-union, defects in bone or cartilage caused by the removal of a tumor or cyst, defects in bone or

cartilage associated with a joint prosthesis, osteotomy defects associated with treatment of a mal-alignment or a deformation, defects in bone or cartilage cased by trauma or degeneration, and defects in bone or cartilage associated with a spinal alignment or spinal fusion procedure.

28. The method of claim 25, wherein the administering step includes administering the composition to a bone defect, where the bone defect is selected from the group consisting of oral-maxillofacial, cranio-facial, and periodontal defects.

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(71) Applicant *(for all designated States except US)*: **DEPUY PRODUCTS, INC.** [US/US]; 700 Orthopaedic Drive, Warsaw, IN 46581 (US).

(71) Applicants and
(72) Inventors: **BRUDER, Scott** [US/US]; 33 Crown Point Road, Sudbury, MA 01776 (US). **CLARKE, Rhonda** [US/US]; 2901 Lake John, Winona Lake, IN 46590 (US). **PEDROZO, Hugo** [CO/US]; 2113 E 1200 South, Silver Lake, IN 46982 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **PLOUHAR, Pamela, Lynn** [US/US]; 17411 Battles Road, South Bend, IN 46614 (US).

(74) Agents: **COFFEY, William, R.** et al.; Barnes & Thornburg, 11 South Meridian Street, Indianapolis, IN 46204 (US).

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(54) Title: FLOWABLE OSTEOGENIC AND CHONDROGENIC COMPOSITIONS

(57) Abstract: The repair of a cartilage or bone defect is described using a flowable compositions including a chondrogenic agent or osteogenic agent and a biocompatible carrier that is more fluid at ambient temperatures than at elevated temperatures.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 35/32; A61F 2/00, 2/30
US CL : 424/422, 423, 549; 623/16; 523/115
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST, STN, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,290,558 A (O'LEARY et al) 01 March 1994 (01.03.1994), see whole document.	1-28
Y	US 6,498,172 B1 (CAMERON et al) 24 December 2002 (24.12.2002), see whole document.	1-5, 13-23 and 25-28
Y	US 6,426,332 B1 (RUEGER et al) 30 July 2002 (30.06.2002), see whole document.	6-11 and 13-28

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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